A synthetic vesicle to carry modifier compounds to axonal blocks induced by pathogenic polyQ

https://neurodegenerationresearch.eu/survey/a-synthetic-vesicle-to-carry-modifier-compounds-to-axonal-blocks-induced-by-pathogenic-polyq/

Principal Investigators

GUNAWARDENA, SHERMALI

Institution

STATE UNIVERSITY OF NEW YORK AT BUFFALO

Contact information of lead PI
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USA

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1

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Research Abstract
? DESCRIPTION (provided by applicant): Currently there are no effective treatments/cures for many neurodegenerative diseases, including Huntington’s (HD) and Alzheimer’s disease (AD) affecting an aging baby-boomer generation. Most current therapeutic treatments are aimed at dissolving/dissociating aggregates or plaques and preventing cell death, common

neuropathology seen at the end stage of disease. Such treatments are short-term and have secondary effects that are more devastating than the disease itself. Thus the challenge is to develop therapeutics that efficiently cross the BBB with efficacy only to neurons, targeted to an early pathway during disease so as to cure these diseases Our central hypothesis is that engineered synthetic-vesicles will move on MTs to axonal blocks via associations with endogenous motor proteins. Since work has shown that axonal blocks occur early in disease, our research is focused on engineering synthetic vesicles that can function as therapeutic devices early during disease. Our rationale is that treating an early event in disease progression will cure the disease and stop the propagation of deleterious events, a bold new therapeutic strategy that has not been previously explored. Our long-term research goal is to understand the mechanisms of how axonal transport defects initiate disease pathways and to assess how modifiers against blocks restore transport. For this we will use fundamental knowledge from biology and will transform this information to engineer nanostructures for use in human medicine. In this context our specific aim is to identify how an engineered synthetic nano-vesicle moves and functions in living axons. We have 3 specific objectives, 1: complete the construction of APP-CTF tagged ORM particles, 2: evaluate the motility of APP-CTF-RORM and 3: cage a modifier inside the porous surface of APP-CTF-RORM and evaluate the suppression of axonal blocks. A live imaging and particle analysis method will be used to evaluate particle motility, modifier release, block dissolving and restoration of transport. The rationale for the proposed work is that developing and targeting therapeutic interventions to an early defect will eliminate or modulate downstream deleterious effects that propagate disease stopping cell death. Therefore such a strategy will have a significant impact on stopping the initial progression of disease, which for the first time will lead to a cure. Thus our work is innovative, in our opinion because it represents a new and substantive departure from the status quo, namely developing a therapeutic strategy for an early event in disease progression that is aimed at curing the disease. The proposed research is significant, because it is expected to vertically advance and expand our understanding of how to better develop effective treatments that act early in disease. While such a strategy will significantly alter current treatment approaches against HD, the technology acquired from our integration of engineering/chemistry and neuroscience will dramatically propel the development of numerous successful therapeutic strategies for other neurodegenerative diseases (impact).

Further information available at:

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